REMARKS

1. Explanation of Claim Amendments

Both Pereira et al. (1993) and the Pereira Patent (6,107,460) disclose the sequence of CAP37 (20-44), which differs from the elected species SEQ ID NO:595 at X1 (where CAP37 is NGGRH, identical to our pentapeptide SEQ ID NO:611) and X19 (where CAP37 is Gln).

Pereira et al. (1993) discloses an alignment of CAP37 (20-44) with cathepsin G (20-47) (which has IGSPAGGSR at X1 and G at X19) and elastase (20-44) (ELAS) (which has LRGGH at X1 and A at X19). Cathepsin G (20-47) clearly violates the claim 1 limitation that X1 not exceed 5 amino acids.

Pereira Patent discloses peptide analogs of CAP37 (20-44) and CAP37 (23-42), of which only the former are deemed relevant here. In this series of analogues, none of the mutations affects X1 (i.e., residues 20-24 fo CAP37) or X19 (i.e., residue 44 of CAP37).

Claim 1 previously avoided anticipation by Pereira's CAP37 (20-44) by virtue of requiring compliance with at least one of provisos (a)-(e). However, all of these provisos, except for (a) (X19 is Arg or Ala) also excluded our elected species SEQ ID NO:595.

We have decided to delete the present provisos (a)-(e), and instead require that (a) X1 is Arg, Lys, amino acids 1-5 of SID 595, 600, 605 or 606, or one of SID 607-610, 612; and/or (b) X19 is not Gln, Ala or Ser. Consequently, we have also cancelled claims 74-79.

As previously explained, since we positively recited Gln as a choice for X19 (see P12, L2-3, and the definitions of groups 4 and 5 on P11, L22-24), we are entitled under In re Johnson and MPEP 2173.05(i) to exclude it:

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 559 F.2d 1008,

> 1019, 194 USPQ 187, 196 (CCPA 1977) ""[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984).

Likewise, we can limit X1 to whichever positively recited species we wish, such as those set forth in new proviso (a).

Referring to the sequences of claims 27-35, 37, 38 and 40, none has X1=SID 611. More particularly, they have

Claim	SID	X1	X1=SID
27	595	KQGRH	--
28	596	KQGRP	607
29	597	KQGRH	AAs 1-5 of 595
30	598	KQGRP	607
31	599	R	--
32	600	NQGRP	--
33	601	KQGRP	AAs 1-5 of 595
34	602	NQGRP	AAs 1-5 of 600
35	603	KQGRP	607
37	605	RRGGH	--
38	606	RSREY	--
40	593	KQRGP	607

Only two of the aforementioned sequences have X19=Gln(Q).

New claim 82 requires that X1 is amino acids 1-5 of the elected species SEQ ID NO:595. SID 597 also meets this limitation.

New claim 83 requires that X19 is not Gln; claim 84, that it is neither Gln nor Asn (a conservative substitution for Gln per P17, L27); claim 85, that it is Arg (the choice found in elected species SID 595); and claim 86, that it is Arg, Lys or His (the conservative substitution group defined by P17, L26. X19=R in SID 593, 595-599, 600, 603; X19=K in SID 599. Claims

87 and 88 combine limitations.

1.2. In view of the examiner's citation of Pereira, et al. (1993), and in particular the ELAS sequence (seemingly identical to our SID 604), we have cancelled our claim 36, directed to that sequence.

1.3. Claims 89-101 further distinguish Pereira's ELAS sequence. New claim 89 is based on the teaching of P12, L13 that X8 is preferably His or Val (it is His in 595 and Ala in 604). The disclosed conservative substitutions for His are Arg and Lys, and for Val are Leu and Ile. Hence X8=His, Arg, Lys, Val, Leu, Ile. The basis for claims 90-92 is self-evident.

P12, L13-15 teaches that X9 is preferably Ala, Phe or Pro (it is Ala in 595 and Pro in 604, hence Pro has been excised, leaving Ala and Phe. Pro is not a conservative substitution for either Ala or Phe. Those are Gly, Ser, Thr and Met for Ala; Trp and Tyr for Phe. So claim 92 recites that X9=Ala, Gly, Ser, Thr, Met, Phe, Trp, or Tyr. Claims 94-96 are based on the same disclosure.

P12, L15 teaches that X10 is preferably Arg, and the conservative substitutions for Arg are His or Lys. So claim 97 recites X10=Arg, His, Lys, and 98, Arg.

P12, L18 teaches that X17 is preferably Ser, and the conservative subs for Ser are Ala, Gly, Thr and Met. So claim 99 recites X10=Ser, Ala, Gly, Thr, Met, and 100 just Ser.

P12, L18-19 teaches that X18 is preferably Phe, and the disclosed conservative replacements are Trp and Tyr. Claim 101 is to Phe/Trp/Tyr, and 102 just to Phe.

Claim 103 is prompted by the examiner's analysis of the series of analogues disclosed by the Pereira patent.

Claims 104-106 are prompted by the examiner's comments on alanine- and serine-scanning mutagenesis.

Claims 107-136 are based on the disclosure at P12, L6-21 and P17, L25-35.

2. Anticipation Issues

Claims 1, 36, 53, 54, 73-75 and 77 stand rejected as anticipated by Pereira (1993)'s "ELAS" sequence, which as acknowledged is identical to applicant's SID 604.

Accordingly, we have cancelled claim 36, which was specific to SID 604, and amended claim 1 to distinguish both Pereira 91993) and the Pereira Patent by virtue of alternative limitations of X1 and/or X19.

Comparing SID 604 with the elected SID 595, we have (with all differences bold faced, X numbering above SID 595, and the CAP37 numbering and sequence shown below SID 604):

SID

	X	11111111 11
	1	2-345678901234567-89
595		**KQGRH** FCG**GA**LI**HAR**FVM**T**AA**S**C**FR**
604		**LRGGH** FCG**AT**LI**APN**FVM**S**AA**H**C**VA**

	2	3 4
20-44	01234	567890123456789012 34
CAP37		**N**QGRH FCGGALIHARFVMTAASCF**Q**

Pereira'S ELAS sequence is further distinguished by new claims 82-83, further limiting X1 and/or X19, and new 89-101.

3. Obviousness Issues

3.1. Claims 1, 36, 53, 54, 73-75 and 77 stand rejected as obvious over Pereira (1993) in view of the Pereira '460 Patent.

The Examiner argues that certain modifications in the Pereira (1993) sequence corresponding to our SID 44 and to CAP37 (20-44) would be obvious in view of the Pereira Patent, namely

CAP37 position	Our position	Chg to	Basis
41S	X17	R, H, K	col. 8, L36-54
27G	X3	A	col. 9, L8-20
28G	X4	A	ditto
36V	X12	L, I, A	col. 9, L31-41
25F	X2	Y	col. 9, L42-46
35F	X11	Y	ditto
43F	X18	Y	ditto

Even if these suggestions were made, none are relevant to the claims as amended.

That is, neither Pereira reference discloses or suggest modification of X1 (corresponding to residues 20-24 of CAP37) or of X19 (corresponding to residue 44 of CAP37) and thus does not render claim 1, as amended, obvious (regardless of what is done at X2, X3, X4, X11, X12, X17 and X18).

3.2. Claims 1, 36, 53, 54, 73-75 and 77 stand rejected as obvious over Pereira, et al. (1993) in view of Starling (1997) and further in view of Goffin (1992). As previously explained, Pereira's CAP37 (20-44) do not satisfy either proviso (a) or proviso (b), and hence do not anticipate. Neither Starling nor Goffin teach how to modify Pereira (1993)'s sequences so as to impinge on amended claim 1.

We agree with the examiner that Goffin teaches "alanine-scanning mutagenesis" and Starling teaches "serine scanning mutagenesis".

The Examiner fails to mention is that in the scanning mutagenesis technique, a series of <u>single</u> substitution mutants are generated. Thus, for example, Starling generated separate K78S and H95S mutants of Fas.

Assuming that it would have been obvious in the art to apply alanine- or serine-scanning mutagenesis to Pereira's CAP37 (20-44) peptide or homologous peptides, the result would have been a series of <u>single</u> Ala or Ser substitution mutants of that lead peptide.

No single Ala or Ser substitution mutant of CAP37 (20-44) or ELAS would convert it into a peptide of amended claim 1.

An Ala and Ser scans of CAP37 would result in the following X1's

AQGRH

K**A**GRH

KQ**A**RH

KQG**A**H

KQGR**A**

SQGRH
K**S**GRH
KQ**S**RH
KQG**S**H
KQGR**S**

and those of ELAS in these:

ARGGH
L**A**GGH
LR**A**GH
LRG**A**H
LRGG**A**

SRGGH
L**S**GGH
LR**S**GH
LRG**S**H
LRGG**S**

For proviso (a) of amended claim 1 to be satisfied, X1 must be one of

KGGRH (AAs 1-5 of SID 595)
NQGRP (AAs 1-5 of SID 600)
RRGGH (AAs 1-5 of SID 605)
RSREY (AAs 1-5 of SID 606)
KQGRP (SID 607)
KQGKP (SID 608)
RQGRP (SID 609)
RQGKP (SID 610)
NQGKH (SID 612)
R---- (cp. P12, L8)
K----

If X1 were equal to any of the aforementioned Ala- or Ser-

scanned pentapeptides, then proviso (a) would not be satisfied, and hence proviso (b) (X19 is not Gln, Ala or Ser) would be triggered.

In CAP37 (20-44), X19 is Gln, and in ELAS (20-44), X19 is Ala. Even if CAP37 or ELAS is subjected to Ala or Ser scanning mutagenesis, then X19 can only be Gln, Ala or Ser. All of these are excluded by proviso (b).

Moreover, no combination of alanine or serine substitutions would cause CAP37 (20-44) or ELAS (20-44) to satisfy either of provisos (a) or (b). Proviso (b) bars Ala or Ser, and all of the X1 choices permitted by proviso (a) are lacking in both Ala and Ser.

Since claim 1 requires that at least one of provisos (a) and (b) be satisfied, it follows that claim 1 is not obvious over the stated combination of references.

4. Indefiniteness Issue (OA pp. 3-5)

We have amended claim 1 as suggested by the examiner on pages 15-16 of the action except that we corrected the examiner's inadvertent omission of group 5 residues Arg and Lys from X^9, and we have replaced the former conditions (a)-(e) with new conditions (a)-(b) as explained. We assume that the Examiner considered such revision as overcoming the rejection for alleged lack of clarity.

5. Election/Restriction

Claims 29, 31, 33, 34, 37, 38, and 80 are now listed as withdrawn.

As previously noted the elected species is SID 595, and the examiner extended the search and examination to SID 604.

Claim 1 defines an allowable generic claim, and hence claims 29 (SID 597), 31 (SID 599), 33 (SID 601), 34 (SID 602), 37 (SID 605) and 38 (SID 606), drawn to other species within that genus, should be rejoined.

Claims 57, 58, 80 and 81, drawn to methods of use of the peptide of claim 1, should be rejoined pursuant to MPEP 821.04.

Respectfully submitted,

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